Illuminating the Structure and Self-Assembly of Alzheimer's Fibrils

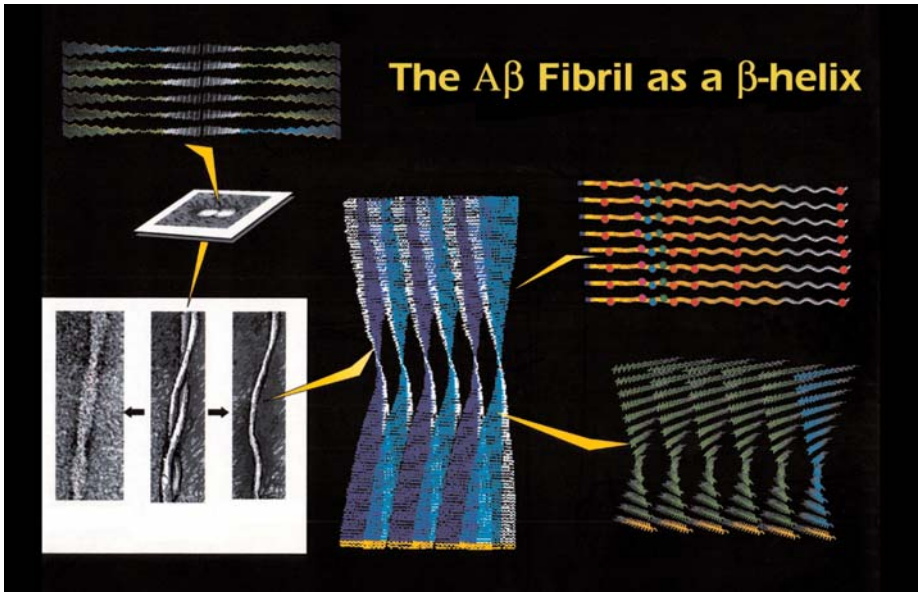
ARGONNE NATIONAL LABORATORY

Challenge

In patients with Alzheimer's disease, a malfunction occurs that produces an abnormal amount of β-amyloid peptides in the brain. Self-assembly of these misfolded peptides manifests itself in the formation of well-organized structures that form fibrils, or plaques, which have been related to the loss of memory and other cognitive functions. Understanding fibril structure and self-assembly and identifying target sites for potential drug candidates have been difficult because detailed structural information on the fibrils has been unavailable.

Argonne Approach

Argonne and University of Chicago researchers are helping battle Alzheimer's and other related diseases (e.g., Huntington's and Prion protein diseases) by using complementary measuring techniques — including electron microscopy (EM), nuclear magnetic resonance (NMR), and small-angle neutron/x-ray scattering (SANS/SAXS) — to perform detailed structural analyses to delineate the processes by which β-amyloid and modified peptides form fibrils.

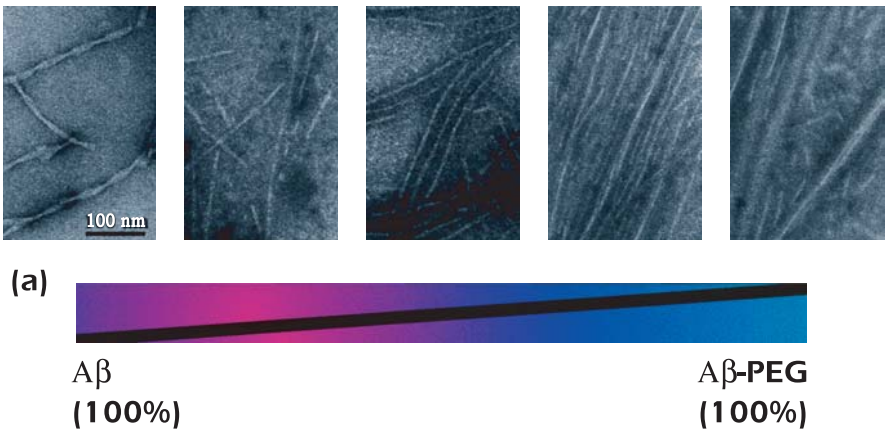


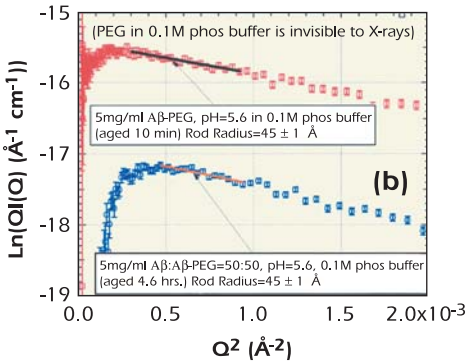
Knowledge about the structure and formation of fibrils at the molecular level may provide insights on how to inhibit fibril growth. Three methods were used for different levels of resolution: (1) EM to directly view the topology of fibrils and their associative properties, (2) SANS and SAXS to follow the self-assembly process at different stages of fibril formation, and (3) solid-state NMR to obtain inter-atomic spacings on noncrystalline forms, showing peptide conformation and their arrangement in the fibril.

A new NMR-pulse sequence that allows for dipolar recoupling between like spins during magic-angle spinning has made it possible to measure interatomic distances in the fibrils with a precision of ± 0.2 angstroms. This capability allowed researchers to determine the peptide conformations and their arrangement in the fibril. SANS and SAXS measurements revealed that the fibrils formed not into single strands, but into rod-like structures. To facilitate these studies, researchers synthesized a truncated peptide and added a polyethylene glycol block at the C-terminus to maintain single-fibril solubility (preventing fibril-fibril association) and to allow fibril formation to become freely reversible and tractable for the first time.

Achievements

Researchers measured the interatomic distances in fibrils with a precision down to ± 0.2 angstroms, making it possible to determine the three-dimensional structure for the entire β-amyloid fibril, which is the largest noncrystalline structure ever characterized. Each peptide was shown to self-assemble in an arrangement of parallel, extended peptide β-strands stacked in a register to form extended sheets. SANS analyses showed that six of these sheets are laminated together by weak sidechain-sidechain interactions to form a super β-helix structure.





Addition of modified PEG-peptides into native fibrils, or plaques, causes reversible dissociation of peptide aggregates: (A) electron micrographs and (B) synchrotron SAXS.

Impact

The new methods developed by Argonne researchers to directly observe the structure, initiation, and propagation of β-amyloid fibril growth can help researchers identify potential drug candidates to prevent or inhibit these diseases.

Another potential application is the use of the β-amyloid fibrils in creating new nanoscale devices, because they combine the strong β-sheet peptide structure of silk with the ability to self-assemble into structurally defined supramolecular arrays.

Collaboration

The University of Chicago

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